The principal functional unit of the central nervous system (CNS) is the neuron. Of all the cells in the body, neurons have the unique ability to receive and transmit information. Neurons of different types and in different locations have distinct properties, including functional roles, distribution of their connections, neurotransmitters used, metabolic requirements, and levels of electrical activity at a given moment. A set of neurons, not necessarily clustered together in a region of the brain, may thus show *selective vulnerability* to various insults because it shares one or more of these properties. Since different regions of the brain participate in different functions, the pattern of clinical signs and symptoms that follow injury depend as much on the region of brain involved as on the pathologic process. Mature neurons are incapable of cell division, so destruction of even a small number of neurons essential for a specific function may leave the individual with a neurologic deficit. Neural progenitor populations are present in certain regions of the brain and have been shown to respond to injury by generating new neurons. For this reason, there is continuing interest in whether expansion of endogenous progenitors or delivery of exogenously derived progenitor cells might be a useful therapeutic approach for repair after injury or in the setting of degenerative diseases.

In addition to neurons the CNS contains other cells, such as *astrocytes* and *oligodendrocytes*, which make up the *glia*. The components of the CNS are affected by a number of unique neurologic disorders and also respond to common insults (e.g., ischemia, infection) in a manner that is distinct from other tissues. We start our discussion of diseases of the CNS with an overview of the patterns of injury of different cells and the reactions of these cells to various insults.

Cellular Pathology of the Central Nervous System

Neurons and glia of the CNS undergo a range of functional and morphologic changes in the setting of injury. Understanding these patterns can be informative about the mechanism of cellular injury and type of disease.

Reactions of Neurons to Injury

Neuronal injury may be an acute process, often a consequence of depletion of oxygen or glucose or trauma, or a slower process, often associated with accumulation of abnormal protein aggregates, as occurs in degenerative disorders of the brain. Neurons require a continuous supply of oxygen and glucose to meet metabolic needs. This satisfies essential physiologic and anatomic requirements of the cells, including maintaining membrane gradients that are essential for action potentials, and supporting the extensive cytoplasmic dendritic arborization of neurons and of axons, which may extend over great distances from the cell body (up to a meter in adults). As most mature neurons are maintained for the life span of an individual, protein turnover and quality have to be carefully regulated to ensure cellular integrity. Not surprisingly, many neurologic diseases result from the injurious effects of accumulated misfolded proteins (*proteinopathies*) (see discussion of protein misfolding and the unfolded protein response in Chapter 2).

MORPHOLOGY

Acute neuronal injury ("red neurons") refers to a spectrum of changes that accompany acute CNS hypoxia/ischemia or other acute insults and reflect the earliest morphologic markers of neuronal cell death (see Fig. 28-13*B*). "Red neurons" are evident by about 12 to 24 hours after an irreversible hypoxic/ischemic insult. The morphologic features consist of shrinkage of the cell body, pyknosis of the nucleus, disappearance of the nucleolus, and loss of Nissl substance, with intense eosinophilia of the cytoplasm.

Subacute and chronic neuronal injury ("degeneration") refers to neuronal death occurring as a result of a progressive disease of some duration, as is seen in certain slowly evolving neurodegenerative diseases such as amyotrophic lateral sclerosis and Alzheimer disease. The characteristic histologic feature is cell loss, often selectively involving functionally related groups of neurons, and reactive gliosis. At an early stage, the cell loss is difficult to detect; the associated reactive glial changes are often the best indicator of neuronal injury. For many of these diseases, there is evidence that cell loss occurs via apoptotic death.

Axonal reaction is a change observed in the cell body during regeneration of the axon; it is best seen in anterior horn cells of the spinal cord when motor axons are cut or seriously damaged. There is increased protein synthesis associated with axonal sprouting. This is reflected in enlargement and rounding up of the cell body, peripheral displacement of the nucleus, enlargement of the nucleolus, and dispersion of Nissl substance from the center to the periphery of the cell (central chromatolysis).

Neuronal damage may be associated with a wide range of subcellular alterations in the neuronal organelles and cytoskeleton. **Neuronal inclusions** may occur as a manifestation of aging, when there are intracytoplasmic accumulations of